Supplemental Online Content

Waring GO IV, Price FW Jr, Wirta D, et al. Safety and efficacy of AGN-190584 in individuals with presbyopia: the GEMINI 1 phase 3 randomized clinical trial. *JAMA Ophthalmol*. Published online March 3, 2022. doi:10.1001/jamaophthalmol.2022.0059

This supplemental material has been provided by the authors to give readers additional information about their work.

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eMethods

Timing of Safety Assessments

Treatment-emergent adverse events were queried at hours 0 (prior to study treatment administration), 0.25, 0.5, 1, 3, 6, 8, and 10 at visits on day 1 (baseline), day 14, and day 30/early exit, and at hours 0 (prior to study treatment administration), 1, and 3 at visits on day 3 and day 7.

Vital signs were measured at hours 0 (prior to study treatment administration) and 1 at visits on day 1 (baseline), day 3, day 7, day 14, and day 30/early exit.

Mesopic, high-contrast, binocular corrected distance visual acuity was measured OD, OS, and binocularly, and pupil diameter was measured in each individual eye, at hours 0 (prior to study treatment administration), 1, 3, 6, 8, and 10 at visits on day 1 (baseline), day 14, and day 30/early exit, and at hours 0 (prior to study treatment administration), 1, and 3 at visits on day 3 and day 7.

Photopic, high-contrast, binocular corrected distance visual acuity was measured OD, OS, and binocularly, and pupil diameter was measured in each individual eye, at hours 0 (prior to study treatment administration), 1, 3, 6, 8, and 10 at visits on day 1 (baseline), day 14, and day 30/early exit, and at hours 0 (prior to study treatment administration), 1, and 3 at visits on day 3 and day 7.

Slit-lamp biomicroscopy was performed at hours 0 (prior to study treatment administration) and 1 at visits on day 1 (baseline), day 3, day 7, day 14, and day 30/early exit.

Intraocular pressure was measured at hours 0 (prior to study treatment administration) and 1 at visits on day 1 (baseline) day 14, and day 30/early exit.

Dilated funduscopic examinations were performed at the screening visit and at hour 10 at the day 30/early exit visit.

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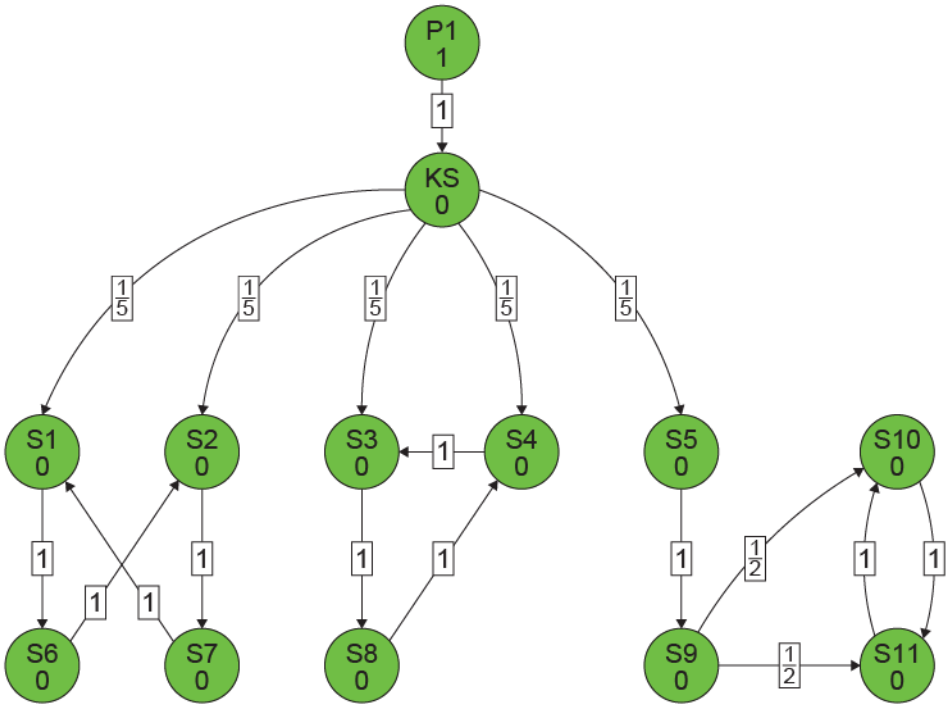
eFigure 1. Graphical Testing Procedure



The overall familywise error rate was controlled at α=0.05 for testing the primary and all secondary efficacy endpoints. Each node represented a hypothesis test for treatment effect on an efficacy endpoint. Hypothesis tests on treatment effect for S1, S2, S3, S4, and S5 were conducted separately at α/5=0.01. If the null hypothesis for testing S1 was rejected, then the hypothesis for S6 was tested. If the null hypothesis for testing S9 was rejected, the hypotheses for S10 and S11 were then tested. P1, primary endpoint; KS, key secondary endpoint; S, secondary endpoint.

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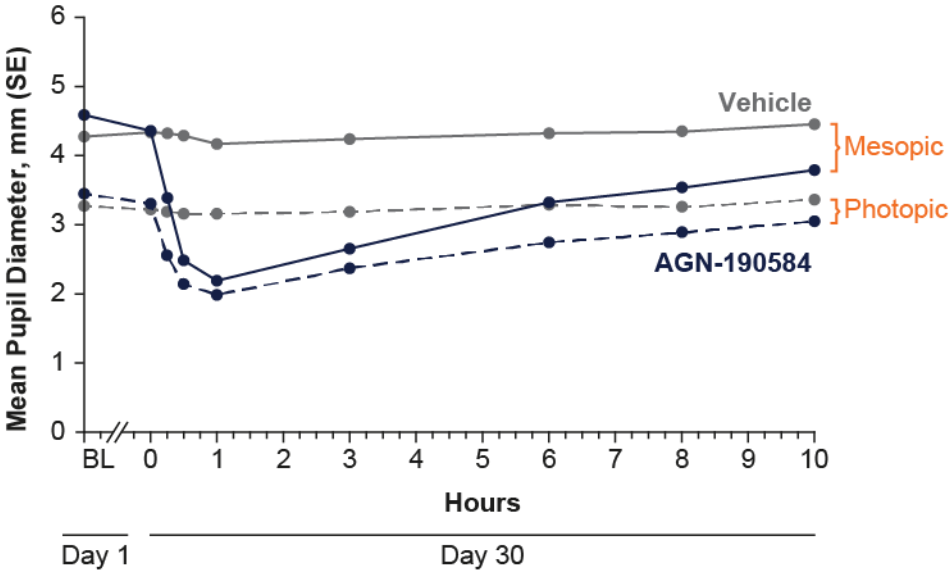
eFigure 2. Pupil Diameter in the Nondominant Eye on Day 30 (Near Vision)



Mesopic and photopic conditions were defined as lighting 10–11 lux and ≥251 lux, respectively, measured at the target. BL, baseline; SE standard error (smaller than the datapoint symbol when not visible on the graph).

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eTable 1. Participant Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age 40 to 55 years (inclusive) at the time of the screening visit	Uncontrolled systemic disease
In good general health at the screening visit, as determined by the investigator	Clinically significant disease state, in the opinion of the examining investigator or designee, in any body system
Subjective complaints of poor near vision that impact activities of daily living, as defined by at least a moderate impact (score ≥3) on at least 1 question on NEI VFQ-25 questions 5 to 7 in the main questionnaire, and Near Vision Subscale questions A3 to A5 in the Appendix of Optional Additional Questions, at the screening visit	Any clinical condition or previous surgery that might affect the absorption, distribution, biotransformation, or excretion of AGN-190584
Emmetrope or non-emmetrope with best distance correction in the range of spherical -4.00 D to +1.00 D inclusively and cylinder ≤ ±2.00 D, with photopic, high-contrast CDVA of 20/25 or better in each eye at the screening and baseline visits	History of cataract surgery, phakic intraocular lens surgery, corneal inlay surgery, radial keratotomy, or any intraocular surgery; however, participants with history of PRK or LASIK with CDVA that meets the inclusion criteria will be allowed to enroll
Photopic, high-contrast CDVA of 20/32 or better in each eye by habitual monofocal correction (either spectacles or contact lenses), or willing to wear new monofocal correction spectacles to achieve photopic, high contrast CDVA of 20/32 or better during the study	Known allergy or sensitivity to the study intervention or its components or other cholinergic agonist medications
Mesopic, high-contrast DCNVA of 20/40 (J3) to 20/100 (J10) in each eye at the screening and baseline visits	Concurrent use of any topical ophthalmic medications (including artificial tears) other than the study intervention during the course of the study
Photopic, high-contrast, near visual acuity correctable to 20/40 (J3+) or better in each eye at the screening and baseline visits	Concurrent use of temporary or permanent punctal plugs, or history of punctal cautery, in one or both eyes
Mesopic pupil diameter <8.0 mm in both eyes at the screening visit	Current enrollment in an investigational drug or device study, or participation in such a study within 30 days of entry into this study
Male or female	Participation in a blood or plasma donation program within 30 days prior to study intervention administration
Capable of giving signed informed consent, which includes compliance with the requirements and restrictions	Presence of any ocular condition that, in the opinion of the investigator, could affect the safety of the participant or interpretation of efficacy parameters (eg, uveitis, retinal detachment)
	Severe dry eye disease (defined as total corneal staining grade of ≥3 on the 5-point Oxford scale and an OSDI score of >33) at the screening visit
	Corneal abnormalities (including keratoconus, corneal scar, Fuchs' endothelial dystrophy, guttata, or edema) in either eye that are likely to interfere with visual acuity
	Narrow iridocorneal angles (Shaffer grade ≤2 on gonioscopy examination), history of angle-closure glaucoma, or previous iridotomy
	History of iris trauma, Adie's tonic pupil, abnormal pupil shape in either eye, or anisocoria >1 mm between pupils under mesopic conditions at the screening visit

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listed in the informed consent form and in the study protocol Written informed consent from the participant or a legally authorized representative has been obtained prior to any study-related procedure Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information for the United States) Able (as assessed by the investigator) and willing to follow study instructions, and likely to complete all required study visits	Lens opacity in either eye that is determined to cause significant disturbance of the central visual axis on screening biomicroscopy Diagnosis of any type of glaucoma or ocular hypertension Use of bifocal or multifocal spectacles or contact lenses for habitual correction during the study; participants willing to wear study-provided monofocal correction (either spectacles or contact lenses) during the study can be enrolled Abnormal and clinically significant results, according to the investigator or designee, on physical/ophthalmic examination or medical history Females who are pregnant, nursing, or planning a pregnancy during the study Females of childbearing potential and males with partners of childbearing potential who do not agree to use reliable contraception during the study The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study

CDVA, corrected distance visual acuity measured at 4 m; DCNVA, distance-corrected near visual acuity measured at 40 cm; LASIK, laser-assisted in situ keratomileusis; NEI VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; OSDI, Ocular Surface Disease Index; PRK, photorefractive keratectomy.

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eTable 2. Preplanned Subgroup Analyses of Primary and Key Secondary Efficacy Endpoints

	Primary Endpoint			Key Secondary Endpoint		
	Proportion of Participants With ≥3-Line Gain in Mesopic, High-Contrast, Binocular DCNVA at Day 30, Hour 3			Proportion of Participants With ≥3-Line Gain in Mesopic, High-Contrast, Binocular DCNVA at Day 30, Hour 6		
Subgroup	**AGN-190584 % (n/N)[a]**	**Vehicle % (n/N)[a]**	**Difference Between Treatment Groups %**	**AGN-190584 % (n/N)[a]**	**Vehicle % (n/N)[a]**	**Difference Between Treatment Groups %**
Age						
≤50 years	29.3 (27/92)	12.9 (12/93)	16.4	18.5 (17/92)	11.8 (11/93)	6.7
>50 years	32.4 (23/71)	1.5 (1/67)	30.9	18.3 (13/71)	4.5% (3/67)	13.8
Baseline mesopic, high-contrast, binocular DCNVA						
20/40 to 40/60 inclusive	24.2 (16/66)	6.5 (4/62)	17.8	13.6 (9/66)	8.1 (5/62)	5.6
Worse than 20/60	35.1 (34/97)	9.2 (9/98)	25.9	21.6 (21/97)	9.2 (9/98)	12.5
Iris color						
Brown	34.6 (27/78)	10.4 (8/77)	24.2	25.6 (20/78)	10.4 (8/77)	15.3
Nonbrown	27.1 (23/85)	6.0 (5/83)	21.0	11.8 (10/85)	7.2 (6/83)	4.5
Emmetrope status						
Emmetrope	31.2 (39/125)	8.9 (11/123)	22.3	18.4 (23/125)	9.8 (12/123)	8.6
Non-emmetrope	28.9 (11/38)	5.4 (2/37)	23.5	18.4 (7/38)	5.4 (2/37)	13.0

[a] Missing data were imputed as failure to achieve ≥3-line gain.
DCNVA, distance-corrected near visual acuity.

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eTable 3. Distribution of Mesopic and Photopic High-Contrast, Binocular Distance-Corrected Near Visual Acuity (Snellen Equivalent) on Day 30

	Participants, n (%)[a]							
	AGN-190584 (N=161)				Vehicle (N=153)			
Visual Acuity	**Hour 0**	**Hour 1**	**Hour 3**	**Hour 6**	**Hour 0**	**Hour 1**	**Hour 3**	**Hour 6**
Mesopic DCNVA								
20/40 or better	40 (24.8)	110 (68.3)	89 (55.3)	69 (42.9)	25 (16.3)	52 (34.0)	48 (31.4)	37 (24.2)
20/50	43 (26.7)	34 (21.1)	41 (25.5)	45 (28.0)	48 (31.4)	47 (30.7)	43 (28.1)	46 (30.1)
20/63	34 (21.1)	12 (7.5)	23 (14.3)	27 (16.8)	45 (29.4)	32 (20.9)	38 (24.8)	44 (28.8)
20/80 or worse	44 (27.3)	5 (3.1)	8 (5.0)	20 (12.4)	35 (22.9)	22 (14.4)	24 (15.7)	26 (17.0)
Photopic DCNVA								
20/40 or better	107 (66.5)	149 (92.5)	136 (84.5)	123 (76.4)	103 (67.3)	113 (73.9)	110 (71.9)	113 (73.9)
20/50	21 (13.0)	8 (5.0)	19 (11.8)	24 (14.9)	24 (15.7)	26 (17.0)	27 (17.6)	22 (14.4)
20/63	15 (9.3)	2 (1.2)	5 (3.1)	12 (7.5)	20 (13.1)	11 (7.2)	11 (7.2)	14 (9.2)
20/80 or worse	18 (11.2)	2 (1.2)	1 (0.6)	2 (1.2)	6 (3.9)	3 (2.0)	5 (3.3)	4 (2.6)

[a] Analysis based on observed data.
DCNVA, distance-corrected near visual acuity.

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eTable 4. All Reported Treatment-Emergent Adverse Events, Number (%) of Participants (Safety Population)

Adverse Event	AGN-190584 (N=163)	Vehicle (N=159)
Abdominal discomfort	1 (0.6)	0 (0.0)
Acne	1 (0.6)	0 (0.0)
Alopecia	1 (0.6)	0 (0.0)
Arthropod bite	1 (0.6)	0 (0.0)
Asthenopia	2 (1.2)	0 (0.0)
Blood pressure diastolic increased	1 (0.6)	0 (0.0)
Blood pressure increased	1 (0.6)	1 (0.6)
Bradycardia	1 (0.6)	0 (0.0)
Chalazion	1 (0.6)	0 (0.0)
Conjunctival disorder	0 (0.0)	1 (0.6)
Conjunctival edema	0 (0.0)	1 (0.6)
Conjunctival hemorrhage	0 (0.0)	1 (0.6)
Conjunctival hyperemia	4 (2.5)	4 (2.5)
Contusion	1 (0.6)	0 (0.0)
Dental caries	1 (0.6)	0 (0.0)
Dermal cyst	1 (0.6)	0 (0.0)
Diverticulum	0 (0.0)	1 (0.6)
Dry eye	2 (1.2)	3 (1.9)
Dyschromatopsia	1 (0.6)	0 (0.0)
Dyspepsia	0 (0.0)	1 (0.6)
External ear pain	1 (0.6)	0 (0.0)
Eye irritation	4 (2.5)	1 (0.6)
Eye pain	4 (2.5)	1 (0.6)
Eye pruritus	0 (0.0)	1 (0.6)
Facial paralysis	0 (0.0)	1 (0.6)
Foreign body sensation in eyes	1 (0.6)	0 (0.0)
Glare	1 (0.6)	0 (0.0)
Head injury	0 (0.0)	1 (0.6)
Headache	23 (14.1)	15 (9.4)
Hemorrhoids	1 (0.6)	0 (0.0)
Hypertension	2 (1.2)	1 (0.6)
Lacrimation decreased	1 (0.6)	0 (0.0)
Lacrimation increased	4 (2.5)	0 (0.0)
Large intestine benign neoplasm	1 (0.6)	0 (0.0)
Malaise	1 (0.6)	0 (0.0)
Meibomian gland dysfunction	1 (0.6)	1 (0.6)
Migraine	0 (0.0)	1 (0.6)
Migraine with aura	1 (0.6)	0 (0.0)
Nausea	4 (2.5)	0 (0.0)
Paraesthesia	1 (0.6)	0 (0.0)
Paranasal sinus discomfort	1 (0.6)	0 (0.0)
Peptic ulcer	0 (0.0)	1 (0.6)
Pharyngitis streptococcal	1 (0.6)	0 (0.0)
Photophobia	2 (1.2)	0 (0.0)
Premenstrual headache[a]	0 (0.0)	1 (0.8)
Punctate keratitis	1 (0.6)	5 (3.1)
Rash	0 (0.0)	1 (0.6)
Seasonal allergy	1 (0.6)	1 (0.6)

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Sinus headache	0 (0.0)	1 (0.6)
Sinusitis	1 (0.6)	1 (0.6)
Skin abrasion	1 (0.6)	0 (0.0)
Tinnitus	1 (0.6)	0 (0.0)
Upper limb fracture	0 (0.0)	1 (0.6)
Upper-airway cough syndrome	1 (0.6)	0 (0.0)
Vision blurred	4 (2.5)	2 (1.3)
Visual field defect	1 (0.6)	0 (0.0)
Visual impairment	7 (4.3)	1 (0.6)
Vital dye staining cornea present	1 (0.6)	2 (1.3)
Vitreous floaters	1 (0.6)	0 (0.0)
Vomiting	1 (0.6)	0 (0.0)
Overall (any adverse event)	57 (35.0)	37 (23.3)

[a] Event and incidence rate specific to females.

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